CERTIFICATE OF MAILING

I hereby certify that the attached DECLARATION OF RICHARD HEUSER, M.D. was delivered to the Assistant Commissioner for Patents by the undersigned from Arrow Intellectual Property Services, 2001, Jefferson Davis Highway, Suite 602, Arlington, Virginia 22202, by hand carrying said DECLARATION to Art Unit 1646, Crystal Plaza 1, Tenth Floor, Attention: Examiner Elizabeth C. Kemmerer this 17th day of June, 2003.

Dated: June 17, 2003

Ann Rutledge

Printed Name: Ann Rutledge

ARROW INTELLECTUAL PROPERTY SERVICE

ocket No.: 1000-10-CO1

rial No.: 09/836,750

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ue Date: - - -

e Patent Office acknowledges, and has stamped hereon, the date of receipt the Items check below:

- Transmittal Letter
- Application – Trademark
- Application – Patent Specification Total Pgs_____
- Total Claims____ Ind. Claims ____ Total Pgs_____
- Fee: $_____
- Abstract Total Pgs:_____
- Drawings: Formal __ Informal ___ Total Pgs_____
- Declaration/Oath/Power of Attorney Total Pgs _____
- Assignment Fee: $:_____
- Request for Non-Publication
- Information Disclosure Statement
- Form PTO-1449 References ____ Total No _____
- Request for Extension of Time Fee: $_____
- Amendment/Response
- Declaration of Richard Heuser
- Brief/Reply Brief/Notice of Appeal
- Fee-Base/Maintenance Fee: $_____
- Check No. _____ Fee: $_____
- _____
- _____

COPY

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT: James P. Elia	)	
	)	
SERIAL NO.: 09/836,750	)	EXAMINER: E.C. Kemmerer, Ph.D.
	)	
FILED: April 17, 2001	)	
	)	GROUP ART UNIT: 1646
FOR: METHOD AND APPARATUS	)	
FOR INSTALLATION OF	)	
DENTAL IMPLANT	)	

DECLARATION OF RICHARD HEUSER, M.D.

I, Richard Heuser, declare as follows:

1. I have offices at 525 North 18th Street, Suite 504, Phoenix, Arizona 85006.

2. My Curriculum Vitae is attached hereto as Exhibit A.

3. I have read and understood the disclosures of the above-referenced patent application at page 20, line 10 through page 21, line 15; and page 44, line 19 through page 46, line 16. A copy of such disclosures is attached hereto as Exhibit B.

4. I note that the disclosures referenced in above Paragraph 3 relate to using a growth factor for promoting the growth of soft tissue and, more specifically, to a method of using a growth factor for growing muscle in a human heart.

5. I am aware of and have considered the definition of *growth factor* in the specification of the above-referenced patent application at page 20, line 10 through page 21, line 15. Such definition is set forth in Exhibit C along with a definition from the medical dictionary, MEDLINE plus: Merriam-Webster Medical Dictionary. A service of the U.S. NATIONAL LIBRARY OF MEDICINE and the NATIONAL INSTITUTES OF HEALTH. I find that the dictionary definition is consistent with that contained at page 20, line 10 through page 21, line 15 of the above-referenced patent application. I believe that both definitions are appropriate for use in the field of tissue growth and would be understood by one skilled in the medical arts. Accordingly, I am adopting and utilizing the definition contained in the patent application throughout this declaration.

6. I have read and understood the claims set forth in Exhibit D and have been informed that such claims will be presented to the Patent and Trademark Office in the near future.

7. The materials included in attached Exhibit E illustrate that placement of a growth factor in a human patient causes muscle growth in a heart. These materials report work performed by reputable, skilled scientists and reputable organizations in the medical arts. Consequently, I believe that these reports would be recognized as clearly valid by one of ordinary skill in the medical arts because they report the results of scientific tests conducted by competent, disinterested third parties with use of proper scientific controls.

8. Based upon above Paragraphs 3-7, it is my opinion that introducing a growth factor into a human patient will predictably cause new muscle growth in the heart of the patient.

9. Based upon above Paragraphs 3-6, it is my opinion that one skilled in the medical arts, armed with the knowledge in such paragraphs, would be able to practice the method set forth in Exhibit D without need for resorting to undue experimentation.

10. Declarant states that the above opinion was reached independently.

Declarant understands that (1) any willful false statements and the like made herein are punishable by fine or imprisonment, or both (18 U.S.C. 1001) and may jeopardize the validity of the application or any patent issuing thereon, and (2) that all statements made of Declarant's own knowledge are true and that all statements made on information and belief are believed to be true.

Further Declarant sayeth not.

Date: 6/5/13

Richard Heuser

EXHIBIT A

CURRICULUM VITAE

Curriculum Vitae
Richard Ross Heuser, M.D., F.A.C.C., F.A.C.P.

ADDRESS:

525 North 18th Street, Suite 504
Phoenix, Arizona 85006
(602) 234-0004
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phoenixheart@earthlink.net

EDUCATION:

1969 - 1972	University of Wisconsin Honors in Chemistry Phi Beta Kappa Evan Helfaer Scholarship in Chemistry
1972 - 1976	University of Wisconsin School of Medicine Graduation with Honors – May 1976 Alpha Omega Alpha Evan Helfaer Scholarship in Medicine

POST GRADUATE TRAINING:

1976 - 1977	Internship in Medicine The Johns Hopkins Hospital Baltimore, Maryland
1977 - 1979	Residency in Medicine The Johns Hopkins Hospital Baltimore, Maryland
1979 - 1981	Fellowship in Cardiology The Johns Hopkins Hospital Baltimore, Maryland

LICENSURE:

State of Arizona, License #19703
State of New Mexico, License #83-220

EMPLOYMENT:

December 2002 - Present	Director of Cardiovascular Research St. Joseph's Hospital and Medical Center Phoenix, Arizona
April 2001 - Present	Cardiac Cath Lab Director St. Luke's Medical Center, Phoenix, Arizona
June 2000 - Present	Medical Director Discovery Alliance, Phoenix, Arizona
1998 - June 2000	Director Phoenix Research Center, Phoenix, Arizona

April 1997 - Present	Medical Director Phoenix Heart Center, Phoenix, Arizona
December 1999 - Present	Director of Research St. Luke's Medical Center, Phoenix, Arizona
April 1997 - December 1999	Director of Research and Education Phoenix Regional Medical Center, Phoenix, Arizona
April 1990 - April 1997	Director of Research and Education Arizona Heart Institute, Phoenix, Arizona
July 1983 - April 1990	Private Practice New Mexico Heart Clinic, Albuquerque, New Mexico
July 1982 - June 1983	Private Practice Houston Cardiovascular Associates, Houston, Texas
June 1981 - July 1982	Instructor in Medicine, Cardiology The Johns Hopkins Hospital, Baltimore, Maryland

PROFESSIONAL APPOINTMENTS:

1981 - July 1982	Instructor in Medicine - Cardiology Division of Cardiology The Johns Hopkins Hospital, Baltimore, Maryland
July 1982 - June 1983	Instructor in Medicine, Cardiology Baylor College of Medicine, Houston, Texas
July 1983 - February 1990	Director, Interventional Cardiology New Mexico Heart Clinic, Albuquerque, New Mexico
April 1984 - June 1986	Clinical Assistant Professor of Medicine University of New Mexico, Albuquerque, New Mexico
	Director, Medical Residency Program New Mexico Heart Clinic, Albuquerque, New Mexico
June 1986 - April 1990	Clinical Associate Professor of Medicine University of New Mexico, Albuquerque, New Mexico
May 1996 - April 1997	Director, Interventional Cardiology Arizona Heart Institute Foundation, Phoenix, Arizona
Sept 1995 - December 1999	Medical Director - Cardiac Catheterization Laboratory Phoenix Regional Medical Center, Phoenix, Arizona
December 1990 - Present	Clinical Associate Professor of Medicine University of Louisville, Louisville, Kentucky
April 1990 - April 1997	Director of Research and Education Arizona Heart Institute Foundation, Phoenix, Arizona

April 1997 - December 1999 Director of Research and Education
Phoenix Regional Medical Center, Phoenix, Arizona

BOARD MEMBERSHIPS:

American Board of Internal Medicine
American Board of Cardiovascular Diseases, Diplomat
American Board of Interventional Cardiovascular Diseases, Diplomat

PROFESSIONAL MEMBERSHIPS:

Fellow, American College of Angiology
Fellow, American College of Cardiology
Fellow, American College of Physicians
Fellow, of the American Heart Association
Fellow, American Society of Cardiovascular Interventions
Fellow, International Society of Cardiovascular Interventions
Fellow, Society for Cardiac Angiography and Interventions
Member, American Association for the Advancement of Science
Member, American Heart Association
Member, American Medical Association
Member, Houston Cardiology Society
Member, Houston Society of Internal Medicine
Member, International Andreas Grüntzig Society
Member, International Network of Interventional Cardiology
Member, International Society for Carotid Artery Therapy
Member, International Society for Minimally Invasive Cardiac Surgery
Member, New Mexico Medical Society
Member, Harris County Medical Society
Member, Texas Medical Association
Member, National Register's Who's Who in Executives and Professionals
Member, Who's Who in Medicine and Healthcare 2002-2003

CLINICAL ADVISORY BOARDS:

Advanced Cardiovascular Systems
USCI
Mansfield Scientific Interventional Board
Medtronic Interventional Vascular
Scientific Advisory Board of International Society of Heart Failure

EDITORIAL BOARDS:

Catheterization and Cardiovascular Diagnosis
Journal of Endovascular Surgery
Cardiovascular Research Foundation/Society or Cardiac Angiography and Interventions
Abstract Grader TCT

DATA SAFETY BOARDS:

- ICEM Data Safety Monitoring Board

- Abbott Laboratories Data Safety Monitoring Board for Drug Coated Stent Program, PREFER, A Perspective STUDY to Evaluate the Safety and Efficacy of the ABT-578 coated BiodivYsio® Stent for the Reduction of Resetnosis

CONSULTANT TO:

Editors of the *Annals of Internal Medicine*
Editors of *Catheterization and Cardiovascular Diagnosis*
Editors of *Circulation*
Editors of the *Journal of Invasive Cardiology*
Editors of the *American Journal of Cardiology*
Editors of *Web M.D.*
Annual Scientific Session Program Committee of the American College of Cardiology
Annual Scientific Session Program Committee of the American College of Cardiology
Abstract Advisor for Angioplasty; Stents
Annual International Symposium of Transcatheter Cardiovascular Therapeutics
Abstract Grader

DEVICE RESEARCH:

Sub-Investigator	ACS Multi-Link Stent Trial Principal Investigator - ACS RX
Principal Investigator	ACT-One Trial Principal Investigator - Angio-Seal Trial
Principal Investigator	Balloon Expandable Intraluminal Stent for Subtotally Occluded Iliac Arteries
Principal Investigator	Bard® Memotherm Carotid Stent Study
Principal Investigator	BARRICADE Trial - The Barrier Approach to Restenosis: Restrict Intima and Curtail Adverse Events (JOMED JOSTENT)
Principal Investigator	BEST Trial
Principal Investigator	BetaCath System Trial
Principal Investigator	Boehringer Ingelheim Pharmaceutics Protocol Comparing Micardis and COZAAR
Principal Investigator	CABERNET Clinical Trial - Carotid Artery Revascularization using the Boston Scientific EPI FiltreWire EX™ and the EndoTex™ NexStent™
Principal Investigator	CADILLAC Trial
Principal Investigator	CAPRICORN Trial
Principal Investigator	CAPTIVE - Cardioshield Application Protects During Transluminal Intervention of Vein Grafts by Reducing Emboli
Principal Investigator	CARDIOMETRICS
Principal Investigator	Carotid Wallstent Trial
Principal Investigator	CAVEAT II Trial
Principal Investigator	Clinical Investigation of the Magnum Wire vs. Standard Guide Wires during Total Occlusion Angioplasty
Principal Investigator	Cook GR II Trial
Principal Investigator	CORDIS Nitinol Carotid Stent And Delivery System for the Treatment of Obstructive Carotid Artery Disease
Principal Investigator	Cordis Carotid Randomized Sapphire
Principal Investigator	Cordis Bilateral AAA Device & Delivery System
Principal Investigator	(CATS) Safe-Steer™ Wire System Coronary Artery Total Occlusion Study
Principal Investigator	CREDO Trial
Principal Investigator	Novoste CUP Trial
Principal Investigator	CVD Accucath Infusion Catheter
Principal Investigator	Duett Closure Devise
Principal Investigator	EndoSonics Cath scanner Oracle - PTCA Catheter

Principal Investigator EPI FilterWire EX™ System During Transluminal Intervention of Saphenous Vein Grafts
Principal Investigator Extra Stent
Principal Investigator GREAT - Guided Radio Frequency Energy Ablation of Total Occlusions Using the Safe Cross™ Radio Frequency Total Occlusion Crossing System
Principal Investigator GRIP - Guided Radio Frequency in Peripheral Total Occlusions using the Safe-Cross™ Radio Frequency (RF) Total Occlusion (TO) Crossing System
Principal Investigator HIPS Trial
Principal Investigator Human Percutaneous Laser Angioplasty of the Coronary Arteries
Principal Investigator Johnson & Johnson Intracoronary Stent Program Supplement #27 "New" Delivery System
Principal Investigator Kensey Nash Hemostatic Puncture Closure Device
Principal Investigator Mansfield-Boston Scientific Strecker Coronary Stent
Principal Investigator Medtronic AVE S7 with Discrete Technology Coronary Stent System
Principal Investigator Medtronic AVE S7 Coronary Stent Registry
Principal Investigator MOBILE Trial - More Patency with Beta for In-Stent Restenosis in the Lower Extremities Trial IDE #G010295; Protocol D00789 Rev B dated 12/01
Principal Investigator NIR Stent Trial
Principal Investigator Neurex/Elan Pharmaceuticals Trial
Principal Investigator PAMI Stent Trial
Principal Investigator Paragon Stent
Principal Investigator Paris Radiation Trial
Principal Investigator PaS Trial
Principal Investigator Percutaneous Coronary Angioscopy in Unstable Angina
Principal Investigator Percutaneous Recanalization of Stenotic Human Coronary Arteries with Balloon Expandable Intracoronary Stents
Principal Investigator Percutaneous Recanalization of Stenotic Human Saphenous Vein Bypass Graft with Balloon Expandable Intraluminal Stents
Principal Investigator Percutaneous Thermal Balloon Angioplasty
Principal Investigator PMR Trial
Principal Investigator Pravastatin or Atorvastatin Evaluation and Infection Therapy (Prove It)
Principal Investigator Presto Trial
Principal Investigator RAVES Trial
Principal Investigator RESCUE Trial
Principal Investigator SAFER - Saphenous Vein Graft Angioplasty Free of Emboli Randomized Study Using the PercuSurge Guard Wire™ System
Principal Investigator SAVED Trial
Principal Investigator Schering-Plough Phase III Study of SCH 58235 in addition to Pravastatin compared to placebo in subjects with primary hypercholesterolemia
Principal Investigator Long-Term, Open-Label, Safety and Tolerability Study of SCH 58235 in Addition to Pravastatin in Patients with Primary Hypercholesterolemia
Principal Investigator Schneider WINS Trial
Principal Investigator SCORES Trial
Principal Investigator Sepracor Study of Norastemizole in Cardiac Compromised Subjects
Principal Investigator SMART Trial (National PI)
Principal Investigator SMART: Post-Approval Study
Principal Investigator SNAPIST - A Phase 2, Safety Study of Systemic Nanoparticle Paclitaxel (ABI-007) For In-Stent Restenosis; IND #63,082
Principal Investigator SOAR - Renal Stent
Principal Investigator Efficacy and Safety Study of the Oral Direct Thrombin Inhibitor H 376/95 Compared with Dose-Adjusted Warfarin (Coumadin) in the Prevention of Stroke and Systemic Embolic Events in Patients with Atrial Fibrillation (SPORTIF V)
Principal Investigator STARS Trial
Principal Investigator START Trial (National PI)
Principal Investigator STRATUS Trial
Principal Investigator STRESS III Trial

Principal Investigator	SUMO Trial
Principal Investigator	(SWING) Sound Wave Inhibition of Neointimal Growth
Principal Investigator	Talent Endoluminal Graft (High Risk & Low Risk)
Principal Investigator	Talent Endoluminal Spring Stent-Graft System
Principal Investigator	Tenax-XR Coronary Stent System
Principal Investigator	TITAN Trial
Principal Investigator	Trimedyne Excimer Laser Assisted Percutaneous Coronary Angioplasty
Sub-Investigator	Trimdyne Percutaneous Eclipse Holmium Laser Coronary Angioplasty
Principal Investigator	VeGAS 2 Trial
Principal Investigator	Velocity Trial Principal Investigator - Venus Stent
Co-Investigator	WALLSTENT Study
Principal Investigator	WIKTOR Coronary Stent

PHARMACOLOGY RESEARCH:

Principal Investigator	Abbott rUK Trial
Principal Investigator	Ajinimoto Pharmaceuticals Double-Blind Placebo-Controlled Study of AT-1015 in Patients with Intermittent Claudication due to peripheral arterial disease
Sub-Investigator	Amgen, Inc. Anakinra Trial for Rheumatoid Arthritis
Principal Investigator	Astra Zeneca Pharmaceutical Trial to Evaluate the Safety and Efficacy of XXXX and Atorvastatin
Principal Investigator	Astra Zeneca Trial Open Label Dose Comparison Study to Evaluate the Safety and Efficacy of Rosuvastatin versus Atorvastatin, Pravastatin, and Simvastatin in Subjects with Hypercholesterolemia
Principal Investigator	Parke-Davis and Pfizer Randomized Open-Label Study Comparing the Efficacy of Once Daily Atorvastatin to Simvastatin in Hypercholesterolemic Patients
Principal Investigator	Pilot Study to Evaluate Intracoronary Administration of Activase for the Treatment of Intracoronary Thrombus
Principal Investigator	Artistic Trial
Principal Investigator	AstraZeneca Trial of Niaspan versus New Generation Statin for the Treatment of Type IIB and Type IV Hyperlipidemia
Principal Investigator	AstraZeneca Multicenter Trial for drug (XXX) and Atorvastatin for the Treatment of Hypercholesterolemia
Principal Investigator	BRAVO Trial
Principal Investigator	BioVail Angina & Hypertension Trial
Principal Investigator	CAPRICORN Trial
Principal Investigator	Challenge Trial
Sub-Investigator	Comparison of Lopentol and Omnipaque in Adult Angiocardiography
Sub-Investigator	Comparison of Intravenous Adenosine to Intravenous Placebo in Termination of Spontaneous or Induced Paroxysmal Supraventricular Tachycardia
Principal Investigator	Centocor Chimeric 7E3 Fab
Principal Investigator	COR Therapeutics Randomized Placebo-Controlled Dose Ranging Study of drug (XXXX) in Patients with Atherosclerotic Cardiovascular, Peripheral Vascular, and/or Cerebrovascular Disease
Sub-Investigator	Dose Response Study of Bucindolol in Patients with Congestive Heart Failure
Principal Investigator	Effects of Recombinant Human Superoxide Dismutase in Patients with Acute Myocardial Infarction Subject to Coronary Artery Reperfusion
Sub-Investigator	Eli Lilly - Agitation/Alzheimer's Trial
Principal Investigator	EPILOG Trial
Principal Investigator	ERASER Trial
Principal Investigator	GUSTO Trial
Principal Investigator	A multi-center, randomized, double blind, placebo-and-active controlled Parallel Group Dose-ranging Study of the HMG CoA Reductase Inhibitor, BMS-423526, in the treatment of Hyperlipidemia

Principal Investigator Study Lovastatin XL with MEVACOR in patients with hypercholesterolemia
Sub-Investigator Lovastatin Multi-Center Trial
Principal Investigator Extended Trial of Lovastatin XL for the treatment of hypercholesterolemia
Principal Investigator Multicenter Double-Blind Placebo controlled trial of drug (XXXX) in patients with Type 2 Diabetes and Congestive Heart Failure
Principal Investigator Effect of LDL-Cholesterol Lowering Beyond Currently Recommended Minimum Targets on coronary heart disease (CHD) Recurrence in patients with Pre-Existing CHD
Principal Investigator A Double-Blind, Multi-Center, Randomized, Placebo-Controlled, Parallel Group Dosing Study Evaluating the Effects of Nebivolol on Blood Pressure in Patients with Mild to moderate Hypertension, NEB 302
Principal Investigator Parallel Group Extension Study to Determine the Safety and Efficacy of Long-Term Nebivolol Exposure in Patients with Mild to Moderate Hypertension NEB 306,
Sub-Investigator NeoTherapeutics Alzheimer's Disease 2000
Sub-Investigator NeoTherapeutics Alzheimer's Disease 2001
Principal Investigator OCTAVE Trial
Sub-Investigator OCTAVE Trial
Principal Investigator Pfizer Phase II Multicenter, double-blind placebo controlled randomized parallel group dose ranging study of the safety of CP529,414 soft-gel capsules
Principal Investigator PLAC Trial
Principal Investigator Protocol 073 Trial
Principal Investigator Knoll Pharmaceutical Double-Blind Randomized Clinical Trial of Slow Release Propafenone (Rythmol-SR®) in the Prevention of Symptomatic Recurrences of Atrial Fibrillation
Principal Investigator PREVAIL - A Phase 2 Multicenter, Double-Blind Placebo-Controlled, Dose-Ranging Study to Evaluate the Safety and Efficacy of BO-653 in Prevention of Post-Angioplasty Restenosis in Stented Lesions
Principal Investigator PROVE-IT TIMI 22 - Pravastatin or Atorvastatin Evaluation and Infection Therapy
Principal Investigator PURSUIT Trial
Principal Investigator QUIET Trial
Principal Investigator RAFT Trial
Principal Investigator REPLACE Randomized Evaluation in PCI Linking Angiomax to reduce Clinical Events
Sub-Investigator Safety and Efficacy Study of Burroughs - Wellcome Tissue Plasminogen Activator in Patients with Acute Myocardial Infarction
Principal Investigator A 6-week, open-label, dose-comparison study to evaluate the safety and Efficacy of Rosuvastatin versus Atorvastatin, Cerivastatin, pravastatin, and Simvastatin in subjects with hypercholesterolemia
Principal Investigator A 48-week, open-label, non-comparative, Multicentre, Phase IIIb study to evaluate the efficacy and safety of the Lipid-Regulating agent Rosuvastatin in the treatment of subjects with Fredrickson Type IIa and Type IIb Dyslipidemia, including Heterozygous Familial Hypercholesterolemia
Principal Investigator SAGE Trial
Sub Investigator Long Term Open Label Safety and Tolerability Study of SCH58235 inn addition to Pravastatin in Patient With Primary Hypercholesterolemia
Principal Investigator Phase III Double-Blind Efficacy and Safety Study SCH58235 (10 mg) in Addition to Pravastatin Compared to Placebo in Subjects with Primary Hypercholesterolemia
Principal Investigator Phase III Open Label Efficacy and Safety Study SCH58235 (10 mg) in Addition to Pravastatin Compared to Placebo in Subjects with Primary Hypercholesterolemia
Principal Investigator Sepracor Protocol Study of Norastemizole in Cardiac Compromised Subjects
Principal Investigator SPORTIF V - Atrial Fibrillation Trial
Principal Investigator SWORD Trial
Principal Investigator Titration-to-Response Trial Comparing Micardis and COZAAR® in Patients with Mild-to-moderate Hypertension

Principal Investigator TNT Trial
Principal Investigator TREND Trial
Sub-Investigator VALDECOXIB Trial
Principal Investigator An Open-Label, Multinational, Multicentre, Extension Trial to Assess the Long-Term Safety and Efficacy of ZD4522 in Subjects in the ZD4522 Clinical Trial Program

BASIC RESEARCH:

1990 - 1993 Systematic assessment of Medtronic balloons and guiding catheters in porcine and canine models. Sponsored by Medtronic, Inc.

1990 - 1993 Determination of radiopacity and torquability of Medtronic vascular catheters in porcine models. Sponsored by Medtronic, Inc.

1992 - 1996 Evaluation of Strecker stent in porcine and canine models. Sponsored by Boston Scientific

Evaluation of Wiktor stent and stent in porcine and canine models. Sponsored by Medtronic, Inc.

Evaluation of NIR stent in porcine models. Sponsored by Cordis Corp.

1990 - 1994 Evaluation of Japan Crescent radiofrequency balloon in porcine model with emphasis on histopathology of heat-produced lesions. Abstract submitted at 1993 AHA Conference.

1993 Evaluation of radiofrequency wire for total coronary occlusions in porcine models: Determining energy limitations. Equipment subsequently licensed to Radius Medical.

1994 - 1997 Training courses for professionals (physicians, engineers, technicians) in techniques and strategies for placement of coronary stents. Five courses sponsored by Johnson & Johnson, Medtronic, Inc. and Cook, Inc.

1997 Efficacy of the Endotex Abdominal Aortic Aneurysm exclusion device in a porcine model gauging ability to exclude renal arteries, ease of placement and radiopacity. Sponsored by Endotex

1998 Use of percutaneous myocardial revascularization in a porcine model. Sponsored by Cardiogenesis Corporation at Stanford University.

1998 - 1999 Utility of radiofrequency (RF) percutaneous myocardial revascularization in acute and chronic porcine model: Histopathology and angiogenesis related to use of RF alone and in combination with growth factor (VEGF). Results presented at Angiogenesis 1999, Washington, DC.

1999 Development and testing of embolic probe device in porcine model (patent pending). Performed at PRMC and separately at Columbia Presbyterian in New York.

1999 Evaluation of the Medtronic carotid and SVG stent in porcine carotid and saphenous vein graft lesions assessing ease of use and 30-day outcome. Sponsored by Medtronic, Inc.

1999 Development and testing of Protector vascular embolic protection device in

porcine model at Mayo Clinic (device patent pending).

1999 Evaluation of ability of intramuscular growth factor to stimulate angiogenesis in rabbit hindlimb model at 30 and 60 days post-procedure. Sponsored by Sulzer Medical.

1999 Use of *Vesseal* device to close porcine peripheral artery tears (patent #6,159,197) Sponsored by Phoenix Heart Center.

PUBLICATIONS:

Bayless TM, **Heuser RR**: Fulminant Colitis. Johns Hopkins Medical Journal 1979 May;144(5): 168-172.

Heuser RR, Achuff SC, Brinker JA: Inadvertent division of an anomalous left anterior descending coronary artery during complete repair of tetralogy of fallot. American Heart Journal 1982 Mar;103(3):430-432.

Fuchs RM, **Heuser RR**, Yin FC, Brinker JA: Limitations of pulmonary wedge V-waves in diagnosing mitral regurgitation. The American Journal of Cardiology 1982 Mar;49(4): 849-854.

Fuchs RM, Brin KP, Brinker JA, Guzman PA, **Heuser RR**, Yin FC: Augmentation of regional coronary blood flow by intraaortic balloon counterpulsation in patients with unstable angina. Circulation 1983 Jul;68(1):117-123.

Alexander EL, Weiss JL, Firestein GS, **Heuser RR**, Leitl G, Wagner Jr HN, Brinker JA, Ciuffo AA, Becker LC: Reversible cold-induced abnormalities in myocardial perfusion and function in systemic sclerosis. Annals of Internal Medical 1986 Nov;105(5):661-668.

Heuser RR: Cardiogenic shock treated by PTCA. Cardiology 1987;4(6):64-66.

Heuser RR, Maddoux GL, Goss JE, Ramo BW, Raff GL, Shadoff N: Coronary angioplasty for acute mitral regurgitation due to myocardial infarction: A nonsurgical treatment preserving mitral valve integrity. Annals of Internal Medical 1987 Dec;107(6):852-855.

Maddoux GL, Goss JE, Ramo BW, Raff GL, **Heuser RR**, Shadoff N, Wilson JN, Deane WM, Hoyt TW, Fowler BN, Gerety RL, Hoffman AR: Left main coronary artery embolism: A case report. Catheterization and Cardiovascular Diagnosis 1987 Nov-Dec;13(6):394-397.

Maddoux GL, Ramo BW, Goss JE, Raff GL, **Heuser RR**, Shadoff N, Leatherman GF, Blake K, Wilson JN, Deane WM, Hoyt TW, Fowler BN, Gerety RL, Sansonetti E: Angina and vasospasm at rest in a patient with an anomalous left coronary system. Catheterization and Cardiovascular Diagnosis 1989 Feb;16(2):95-98.

Goss JE, Ramo BW, Raff GL, Maddoux GL, **Heuser RR**,, Shadoff N, Leatherman GF, Blake K: Power injection of contrast media during percutaneous transluminal coronary artery angioplasty. Catheterization and Cardiovascular Diagnosis 1989 Mar;16(3):195-198.

Heuser RR, Mehta SS: Holmium laser angioplasty after failed coronary balloon dilation: Use of a new solid-state, infrared laser system. Catheterization and Cardiovascular Diagnosis 1991 Jul;23(3):187-189.

Heuser RR, Mehta SS, Strumpf RK, Ponder R: Intracoronary stent implantation via the brachial approach: A technique to reduce vascular bleeding complications. Catheterization and Cardiovascular Diagnosis 1992 Apr;25(4):300-303.

Strumpf RK, Mehta SS, Ponder R, **Heuser RR**: Palmaz-Schatz stent implantation in stenosed saphenous vein grafts: Clinical and angiographic follow-up. American Heart Journal 1992 May;123(5):1329-1336.

Segal J, Kern MJ, Scott NA, King SB, Doucette JW, **Heuser RR**, Ofili E, Siegel R: Alterations of phasic coronary artery flow velocity in humans during percutaneous coronary angioplasty. The Journal of the American College of Cardiology 1992 Aug;20(2):276-286.

Heuser RR: The use of the Holmium: YAG laser in coronary disease: The utility of a unique lensed fiber catheter. The Journal of Interventional Cardiology 1992 Dec;5(4):293-300.

Heuser RR, Eagan JT, Strumpf RK: Angioscopy in coronary interventions. Cardiology Intervention 1992;2(4):23-28.

Santiago O, Diethrich EB, **Heuser RR**, Gustafson G: What is the next step for the application of the Palmaz stent – the abdominal aorta? Angiology 1992;42:267-268.

Heuser RR, Mehta SS, Strumpf RK: The ACS RX™ flow support catheter as a temporary stent for dissection or occlusion during balloon angioplasty: initial experience. Catheterization and Cardiovascular Diagnosis 1992 Sept;27(1):66-74.

Diethrich EB, Santiago O, Gustafson G, **Heuser RR**: Preliminary observations on the use of the Palmaz stent in the distal portion of the abdominal aorta. American Heart Journal 1993 Feb;125(2):490-501.

Heuser RR: Lasers in coronary disease (commentary). Catheterization and Cardiovascular Interventions 1993;28:17.

Eagan JT, Strumpf RK, **Heuser RR**: New treatment approach for chronic total occlusions of saphenous vein grafts: Thrombolysis and intravascular stents. Catheterization and Cardiovascular Diagnosis 1993 May;29(1):62-69.

Heuser RR, Strumpf RK, Diethrich EB, Eagan JT, Hardigan KR: Intraluminal diagnostics, the "guide" to the future. Angiology 1993;44:6.

Heuser RR, Strumpf RK, Eagan JT, Hardigan KR: Experience with four types of coronary stents. Angiology 1993;44:6-7.

Heuser RR: The use of a new wire in a 6-year-old coronary artery occlusion: The Jagwire™ recanalization guidewire. Catheterization and Cardiovascular Diagnosis 1993 Jun;29(2): 173-176.

Heuser RR, Strumpf RK, Hardigan K: Use of the Doppler guidewire for intraluminal diagnosis to facilitate coronary intervention. American Heart Journal 1993 July; 126(1):213-218.

Strumpf RK, **Heuser RR**, Eagan Jr JT: Angioscopy: A valuable tool in the deployment and evaluation of intracoronary stents. American Heart Journal 1993 Nov;126(5):1204-1210.

Heuser RR: Current status of coronary stents: Promises and disappointments. Critical Issues 1993;2:1-13.

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AWARDS & HONORS:

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PATENTS:

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2. Hot Tip Catheter; Patent granted February 20, 2001 Number: 6,190,379
3. Embolism Prevention Device; Patent granted April 2, 2002 Number: 6,364,900
4. Catheter apparatus and Method for Arterializing a Vein; Patent granted October 15, 2002 Number 6,464,665
5. Methods and apparatus for treating body tissues and bodily fluid vessels; Patent granted October 15, 2002 Number: 6,464,681
6. Catheter for Thermal Evaluation of Arteriosclerotic Plaque; Patent granted March 25, 2003 Number: 6,536,949
7. Small Diameter Snare; Patent granted April 29, 2003 Number: 6,554,842

EXHIBIT
B

DISCLOSURES

APPLICATION
SERIAL NO. 09/836,750

EXHIBIT B

DISCLOSURES
APPLICATION SERIAL NO. 09/836,750

PAGE 20, LINE 10 – PAGE 21, LINE 15

Growth factors can be utilized to induce the growth of "hard tissue" or bone and "soft tissues" like ectodermal and mesodermal tissues. As used herein, the term growth factor encompasses compositions and living organisms which promote the growth of hard tissue, such as bone, or soft tissue, in the body of a patient. The compositions include organic and inorganic matter. The compositions can be genetically produced or manipulated. The living organisms can be bacteria, viruses, or any other living organism which promote tissue growth. By way of example and not limitation, growth factors can include platelet-derived growth factor (PDGF), epidermal growth factor (EGF), fibroblast growth factor (acidic/basis (FGF a,b), interleukins (IL's), tumor necrosis factor (TNF), transforming growth factor (TGF-B), colony-stimulating factor (CSF), osteopontin (Eta-1 OPN), platelet-derived growth factor (PDGF), interferon (INF), bone morphogenic protein 1 (BMP-1), and insulin growth factor (IGF). Recombinant and non-recombinant growth factors can be utilized as desired. Bacteria or viruses can, when appropriate, be utilized as growth factors. For example, there is a bacterial hydrophilic polypeptide that self-assembles into a nanometer internal diameter pore to build a selective lipid body. Various enzymes can be utilized for the synthesis of peptides which contain amino acids that control three-dimensional protein structure and growth. Growth factors can be applied in gels or other carriers which regulate the rate of release of the growth factors and help maintain the growth factors and the carrier, at a desired location in the body. Time release capsules, granules, or other carriers containing growth factor can be activated by tissue pH, by enzymes, by ultrasound,

by electricity, by heat, by selected *in vivo* chemicals or by any other selected means to release the growth factor. The carrier can be resorbable or non-resorbable. Or, the growth factor itself can be activated by similar means. Either the carrier or the growth factor can mimic extracellular fluid to control cell growth, migration, and function. The growth factor can be administered orally, systemically, in a carrier, by hypodermic needle, through the respiratory tract, or by any other desired method. The growth factor an also be administered into a capsule or other man-made composition or structure placed in the body. While administration of the growth factor is presently usually localized in the patient's body, circumstances may arise where it is advantageous to distribute a growth factor throughout the patient's body in uniform or non-uniform concentrations. An advantage to growth factors is that they can often, especially when in capsule form or in some other containment system, be inserted to a desired site in the body by simply making a small incision and inserting the growth factor. The making of such small incision comprises minor surgery which an often be accomplished on an out-patient basis. The growth factors can be multifactorial and nonspecific.

PAGE 44, LINE 19 – PAGE 46, LINE 16

Genetic material comprising a portion of a gene, a gene, genes, a gene product (i.e., a composition a gene causes to be produced like, for example, an organ-producing growth factor), growth factor, or an ECM (extracellular matrix) can be used in or on the body to grow an organ to tissue. For example, the vascular epithelial growth factor gene (VEGF) or its growth factor equivalent can be inserted into the body to cause an artery to grow. When insertion of a gene, portion of a gene, gene product, growth factor, or ECM *in vivo* or *ex vivo* is referred to herein in connection with any of the implant techniques of the invention, it is understood that a cell

nutrient culture(s), physiological nutrient culture(s), carrier (s), enhancer(s), promoter(s), or any other desired auxiliary component(s) can be inserted with the gene or at the same location as the gene, growth factor, ECM, etc.

An artery is an organ from the circulatory system. An artery can be grown in the heart, legs, or other areas by injecting a gene or other genetic material into muscle at a desired site. Size, vascularity, simplicity of access, ease of exploitation, and any other desired factors can be utilized in selecting a desired site. The gene is one of several known VEGF genes which cause the production of vascular endothelial growth factors. Several VEGF genes which produce vascular endothelial growth factors are believed to exist because nature intends for there to be several pathways (i.e., genes) which enable the production of necessary growth factors. The existence of several pathways is believed important because if one of the genes is damaged or inoperative, other similar genes can still orchestrate the production of necessary growth factors. VEGF genes are used by the body to promote blood vessel growth. VEGF genes are assimilated (taken in) by muscle cells. The genes cause the muscle cells to make a VEGF protein which promotes the growth of new arteries. VEGF proteins can be made in a lab and injected into a patient intravenously, intraluminally, or intramuscularly to promote the growth of an artery. Or, the genes (or other genetic material) can be applied with an angioplasty balloon, with the assistance of a vector, or by any other method.

It is not always desirable to grow a completely new organ. Sometimes growing a portion of an organ is desirable. For example, in some heart attacks or strokes, a portion of the heart or brain remains viable and a portion dies. An injection of a gene to form cardiac muscle and/or an injection of a gene to form an artery can be utilized to revive or replace the dead portion of the heart. The dead portion of the heart may (or may not) be used as a matrix while the new muscles

and vessels grow. Thus, in this example, a partial new organ is grown in a pre-existing organ. A pacemaker may (or may not) be necessary. A second injection of a gene may (or may not) be necessary to stop cardiac muscle growth once it is completed. Portions of organs throughout the body can similarly be repaired or replaced. It may be necessary to provide gene(s) or growth factor(s) sequentially. For instance, one or more blood vessels are grown by inserting an appropriate gene or other genetic material into a selected area. Second, an appropriate gene or other genetic material is inserted in the selected area to grow a bone or other organ.

The size and shape limitation of the desired structure can come from a containment and boundary contact inhibition phenomenon or by a chemical inhibition.

A variation on the theme of growing a portion of an organ is as follows: a portion of a heart dies. The pericardium is utilized as a scaffold and seeded with cells and/or genes to grow new muscle, and genes (or other genetic material) to grow new arteries. Immediately adjacent the dead cardiac muscle, onto or into the pericardium, the appropriate cells, genes, and/or growth factors (or other genetic material) are placed. Once the new muscle and blood vessels have grown, the function specific tissue can be applied to the damaged portion of the heart and paced, if necessary, to augment cardiac action. If the surgeon desires, the dead muscle can be removed and the new muscle and blood vessels can be surgically rotated into the excised region and secured. This probably can be done endoscopically. In essence, the pericardium is utilized to allow the new muscle wall to grow. The new muscle wall is then transplanted into the damaged heart wall. This procedure utilizes the body as a factor to grow an organ and/or tissue, after which the organ and/or tissue is transplanted to a desired region. On the other hand, the new muscle wall may integrate itself into the old wall and not require transplantation.

EXHIBIT C

DEFINITIONS

EXHIBIT C

DEFINITIONS

PAGE 20, LINE 10 – PAGE 21, LINE 15

Growth factors can be utilized to induce the growth of "hard tissue" or bone and "soft tissues" like ectodermal and mesodermal tissues. As used herein, the term growth factor encompasses compositions and living organisms which promote the growth of hard tissue, such as bone, or soft tissue, in the body of a patient. The compositions include organic and inorganic matter. The compositions can be genetically produced or manipulated. The living organisms can be bacteria, viruses, or any other living organism which promote tissue growth. By way of example and not limitation, growth factors can include platelet-derived growth factor (PDGF), epidermal growth factor (EGF), fibroblast growth factor (acidic/basis (FGF a,b), interleukins (IL's), tumor necrosis factor (TNF), transforming growth factor (TGF-B), colony-stimulating factor (CSF), osteopontin (Eta-1 OPN), platelet-derived growth factor (PDGF), interferon (INF), bone morphogenic protein 1 (BMP-1), and insulin growth factor (IGF). Recombinant and non-recombinant growth factors can be utilized as desired. Bacteria or viruses can, when appropriate, be utilized as growth factors. For example, there is a bacterial hydrophilic polypeptide that self-assembles into a nanometer internal diameter pore to build a selective lipid body. Various enzymes can be utilized for the synthesis of peptides which contain amino acids that control three-dimensional protein structure and growth. Growth factors can be applied in gels or other carriers which regulate the rate of release of the growth factors and help maintain the growth factors and the carrier, at a desired location in the body. Time release capsules, granules, or other carriers containing growth factor can be activated by tissue pH, by enzymes, by ultrasound,

by electricity, by heat, by selected *in vivo* chemicals or by any other selected means to release the growth factor. The carrier can be resorbable or non-resorbable. Or, the growth factor itself can be activated by similar means. Either the carrier or the growth factor can mimic extracellular fluid to control cell growth, migration, and function. The growth factor can be administered orally, systemically, in a carrier, by hypodermic needle, through the respiratory tract, or by any other desired method. The growth factor an also be administered into a capsule or other man-made composition or structure placed in the body. While administration of the growth factor is presently usually localized in the patient's body, circumstances may arise where it is advantageous to distribute a growth factor throughout the patient's body in uniform or non-uniform concentrations. An advantage to growth factors is that they can often, especially when in capsule form or in some other containment system, be inserted to a desired site in the body by simply making a small incision and inserting the growth factor. The making of such small incision comprises minor surgery which an often be accomplished on an out-patient basis. The growth factors can be multifactorial and nonspecific.

MEDLINE PLUS: MERRIAM-WEBSTER MEDICAL DICTIONARY
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> **Growth factor:** a substance (as a vitamin B_{12} or an interleukin) that promotes growth and especially cellular growth

EXHIBIT D

CLAIMS

EXHIBIT D

CLAIMS

Claim X: **A method for growing a new portion of a pre-existing heart comprising the steps of: placing a growth factor in a body of a human patient and growing new muscle in said heart.**

EXHIBIT E

PUBLICATIONS

EXHIBIT E

PUBLICATION INFORMATION SUMMARY

TITLE	AUTHOR	CITATION	DATE	AUTHOR COUNTRY	ROUTE OF ADMINISTRATION	GROWTH FACTOR ADMINISTERED	RESULT
Left Ventricular Electromechanical Mapping to Assess Efficacy of phVEGF165 Gene Transfer for Therapeutic Angiogenesis in Chronic Myocardial Ischemia	Vale	Circulation. 2000; 102:965-974	08/29/00	U.S.	Small incision (minithoracotomy) with syringe injection	VEGF (Gene form)	Repair of damaged portion of heart – Also pertains to new muscle growth
Repair of Infarcted Myocardium by Autologous Intracoronary Mononuclear Bone Marrow Cell Transplantation in Humans	Strauer	Circulation. 2002; 106:1913-1918	10/08/02	Germany	Balloon catheter with injection	Bone Marrow Cells	Repair of dead portion of heart – also pertains to new muscle growth

TITLE	AUTHOR	CITATION	DATE	AUTHOR COUNTRY	ROUTE OF ADMINISTRATION	GROWTH FACTOR ADMINISTERED	RESULT
Viability and differentiation of autologous skeletal myoblast grafts in ischemic cardiomyopathy	Hagege	Lancet 2003 Feb 8; 361 (9356):491-492	2003	France	Injection	Skeletal Muscle Cells	Repair of dead portion of heart; Histological Proof (muscle)
Autologous Cell Transplant Helpful in Ischemic Heart or Legs	Barclay	Medscape Medical News 2000 – Abstract from American Heart Association's 75th Scientific Sessions on 11/18/02, Chicago	11/18/02	U.S.	Surgery with syringe injection	Bone Marrow Cells	Repair of damaged portion of heart – also pertains to new muscle growth
Autologous skeletal myoblasts transplanted to ischemia-damaged myocardium in humans. Histological analysis of cell survival and differentiation	Pagani	J Am Coll Cardiol 2003 Mar 5; 41(5): 879-888	2003	U.S.	Surgery with syringe injection	Skeletal Muscle Cells	Repair of dead portion of heart; Histological Proof (muscle and blood vessels)

Repair of Infarcted Myocardium by Autologous Intracoronary Mononuclear Bone Marrow Cell Transplantation in Humans

Bodo E. Strauer, MD; Michael Brehm, MD; Tobias Zeus, MD; Matthias Köstering, MD; Anna Hernandez, PhD; Rüdiger V. Sorg, PhD; Gesine Kögler, PhD; Peter Wernet, MD

Background—Experimental data suggest that bone marrow–derived cells may contribute to the healing of myocardial infarction (MI). For this reason, we analyzed 10 patients who were treated by intracoronary transplantation of autologous, mononuclear bone marrow cells (BMCs) in addition to standard therapy after MI.

Methods and Results—After standard therapy for acute MI, 10 patients were transplanted with autologous mononuclear BMCs via a balloon catheter placed into the infarct-related artery during balloon dilatation (percutaneous transluminal coronary angioplasty). Another 10 patients with acute MI were treated by standard therapy alone. After 3 months of follow-up, the infarct region (determined by left ventriculography) had decreased significantly within the cell therapy group (from 30±13 to 12±7%, $P=0.005$) and was also significantly smaller compared with the standard therapy group ($P=0.04$). Likewise, infarction wall movement velocity increased significantly only in the cell therapy group (from 2.0±1.1 to 4.0±2.6 cm/s, $P=0.028$). Further cardiac examinations (dobutamine stress echocardiography, radionuclide ventriculography, and catheterization of the right heart) were performed for the cell therapy group and showed significant improvement in stroke volume index, left ventricular end-systolic volume and contractility (ratio of systolic pressure and end-systolic volume), and myocardial perfusion of the infarct region.

Conclusions—These results demonstrate for the first time that selective intracoronary transplantation of autologous, mononuclear BMCs is safe and seems to be effective under clinical conditions. The marked therapeutic effect may be attributed to BMC-associated myocardial regeneration and neovascularization. (*Circulation*. 2002;106:1913-1918.)

Key Words: myocardial infarction ■ cell transplantation, intracoronary ■ angiogenesis ■ bone marrow ■ myogenesis

Remodeling of the left ventricle after myocardial infarction (MI) represents a major cause of infarct-related heart failure and death. This process depends on acute and chronic transformation of both the necrotic infarct region and the non-necrotic, peri-infarct tissue.[1,2] Despite application of pharmacotherapeutics and mechanical interventions, the cardiomyocytes lost during MI cannot be regenerated. The recent finding that a small population of cardiac muscle cells is able to replicate itself is encouraging but is still consistent with the concept that such regeneration is restricted to viable myocardium.[3]

In animal experiments, attempts to replace the necrotic zone by transplanting other cells (eg, fetal cardiomyocytes or skeletal myoblasts) have invariably succeeded in reconstituting heart muscle structures, ie, myocardium and coronary vessels. However, these cells fail to integrate structurally and do not display characteristic physiological functions.[4–7] Another approach to reverse myocardial remodeling is to repair myocardial tissue by using bone marrow–derived cells. Bone marrow contains multipotent adult stem cells that show a high capacity for differentiation.[8–10] Experimental studies have shown that bone marrow cells (BMCs) are capable of regenerating infarcted myocardium and inducing myogenesis and angiogenesis; this leads in turn to amelioration of cardiac function in mice and pigs.[11–14] However, procedures based on this phenomenon remain largely uninvestigated in a human clinical setting.

An investigation of one patient receiving autologous skeletal myoblasts into a postinfarction scar during coronary artery bypass grafting revealed improvement of contraction and viability 5 months afterward.[15] Autologous mononuclear BMCs transplanted in a similar surgical setting showed long-term improvement of myocardial perfusion in 3 of 5 patients and no change in 2 patients.[16] However, such studies entail a surgical approach and are therefore associated with well-known perioperative risks. Moreover, this surgical procedure cannot be used with MI. We therefore looked for a nonsurgical, safer mode for transplanting autologous cells

Received August 2, 2002; accepted August 2, 2002.

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Circulation is available at http://www.circulationaha.org

DOI: 10.1161/01.CIR.0000034046.87607.1C

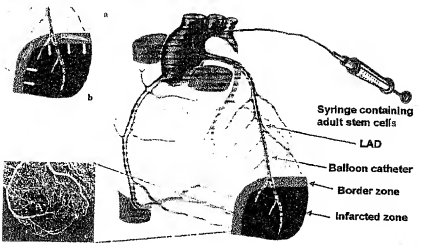

Figure 1. Procedure of cell transplantation into infarcted myocardium in humans. a, The balloon catheter enters the infarct-related artery and is placed above the border zone of the infarction. It is then inflated and the cell suspension is infused at high pressure under stop-flow conditions. b, In this way, cells are transplanted into the infarcted zone via the infarct-related vasculature (red dots). Cells infiltrate the infarcted zone. Blue and white arrows suggest the possible route of migration. c, A supply of blood flow exists within the infarcted zone.[35] The cells are therefore able to reach both the border and the infarcted zone.

into postinfarction tissue. A pilot study from our group demonstrated that intracoronary transplantation of autologous mononuclear BMCs 6 days after MI was associated with a marked decrease in infarct area and an increase in left ventricular (LV) function after 3 and 6 months of follow-up.[17] To confirm these results and validate this promising new therapy for MI, we established a clinical trial involving 20 patients for comparing the safety and bioefficacy of autologous BMC transplantation. All 20 patients underwent standard therapy, and 10 patients received additional intracoronary cell transplantation. All 20 patients were followed up for 3 months.

Methods

Patient Population

All 20 patients had suffered transmural infarction according to World Health Organization criteria with the involvement of the left anterior descending coronary artery (n=4), left circumflex coronary artery (n=3), or right coronary artery (n=13). Mean duration of infarct pain was 12±10 hours before invasive diagnostics and therapy. Patients had to be <70 years old and were excluded if one of the following criteria were met: screening >72 hours after infarction, cardiac shock, severe comorbidity, alcohol or drug dependency, or excessive travel distance to the study center.

After right and left heart catheterization, coronary angiography, and left ventriculography, mechanical treatment was initiated with recanalization of the infarct-related artery by balloon angioplasty (n=20) and subsequent stent implantation (n=19). All patients were monitored in our intensive care unit, and no arrhythmogenic events or hemodynamic impairments were recorded in either patient group.

All 20 patients were briefed in detail about the procedure of BMC transplantation. Informed consent was obtained from 10 patients, who formed the cell therapy group, whereas 10 patients who refused additional cell therapy served as controls. The local ethics committee of the Heinrich-Heine-University, Düsseldorf, approved the study protocol. All procedures conformed to institutional guidelines.

Before taking part in rehabilitation programs, all patients left the hospital with standard medication consisting of acetylsalicylic acid, an ACE inhibitor, a β-blocker, and a statin.

Bone Marrow Aspiration, Isolation, and Cultivation

Seven (±2) days after acute coronary angiography, bone marrow (~40 mL) was aspirated under local anesthesia from ilium of cell therapy patients (n=10). Mononuclear BMCs were isolated by Ficoll density separation on Lymphocyte Separation Medium (BioWhittaker) before the erythrocytes were lysed with H_2O. For overnight cultivation, 1×10^6 BMCs/mL were placed in Teflon bags (Vuelife, Cell Genix) and cultivated in X-Vivo 15 Medium (BioWhittaker) supplemented with 2% heat-inactivated autologous plasma. The next day, BMCs were harvested and washed 3 times with heparinized saline before final resuspension in heparinized saline. Viability was 93±3%. Heparinization and filtration (cell strainer, FALCON) was carried out to prevent cell clotting and microembolization during intracoronary transplantation. The mean number of mononuclear cells harvested after overnight culture was 2.8×10^7; this consisted of 0.65±0.4% AC133-positive cells and 2.1±0.28% CD34-positive cells. All microbiological tests of the clinically used cell preparations proved negative. As a viability and quality ex vivo control, 1×10^5 cells grown in H5100 medium (Stem Cell Technology) were found to be able to generate mesenchymal cells in culture.

Intracoronary Transplantation of BMCs

Five to nine days after onset of acute infarction, cells were directly transplanted into the infarcted zone (Figure 1). This was accomplished with the use of a balloon catheter, which was placed within the infarct-related artery. After exact positioning of the balloon at the site of the former infarct-vessel occlusion, percutaneous transluminal coronary angioplasty (PTCA) was performed 6 to 7 times for 2 to 4 minutes each. During this time, intracoronary cell transplantation via the balloon catheter was performed, using 6 to 7 fractional high-pressure infusions of 2 to 3 mL cell suspension, each of which contained 1.5 to 4×10^6 mononuclear cells. PTCA thoroughly prevented the backflow of cells and at the same time produced a stop-flow beyond the site of the balloon inflation to facilitate high-pressure infusion of cells into the infarcted zone. Thus, prolonged contact time for cellular migration was allowed.[18]

Functional Assessment of Hemodynamics

After 3 months, all 20 patients were followed up by left heart catheterization, left ventriculography, and coronary angiography. Ejection fraction, infarct region, and regional wall movement of the infarcted zone during ejection were determined by left ventriculography. Ejection fraction was measured with Quantcor software (Siemens). To quantify infarction wall movement velocity, 5 axes were placed perpendicular to the long axis in the main akinetic or dyskinetic segment of the ventricular wall. Relative systolic and diastolic lengths were measured, and the mean difference was divided by the systolic duration (in seconds). To quantify the infarct region, the centerline method according to Sheehan was used.[19] All hemodynamic investigations were obtained by two independent observers.

In the cell therapy group before and 3 months after cell transplantation, additional examinations for measuring hemodynamics and myocardial perfusion included dobutamine stress echocardiography, radionuclide ventriculography, catheterization of the right heart, and

TABLE 1. Baseline Characteristics of the Patients

Clinical Data	Cell Therapy	Standard Therapy	*P*
Characteristics			
No. of patients	10	10	...
Age, y	49±10	50±6	NS
Sex	Male	Male	...
Onset of infarction before angioplasty, h	10±8	13±11	NS
Coronary angiography			
No. of diseased vessels	1.7±0.9	2.1±0.7	NS
No. of patients with LAD/LCX/RCA as the affected vessel	4/1/5	0/2/8	...
No. of patients with stent implantation	9	10	...
Laboratory parameters			
Creatinine kinase, U/L	1138±1170	1308±1187	NS
Creatinine kinase-MB, U/L	106±72	124±92	NS
Bone marrow puncture after angioplasty, d	7±2	...	...
Mononuclear bone marrow cells, n ($\times 10^9$)	2.8±2.2	...	...

Values are mean±SD or number of patients.
NS indicates not significant; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; and RCA, right coronary artery.

stress-redistribution-reinjection ^{201}thallium scintigraphy. The contractility index P_{sys}/ESV was calculated by dividing LV systolic pressure (P_{sys}) by end-systolic volume (ESV). Perfusion defect was calculated by scintigraphic bull's-eye technique. Each examination was performed according to standard protocols.

There were no complications or side effects determined in any patient throughout the diagnostic or therapeutic procedure or within the 3-month follow-up period.

Statistical Analysis

All data are presented as mean±SD. Statistical significance was accepted when P was <0.05. Discrete variables were compared as rates, and comparisons were made by χ^2 analysis. Intra-individual comparison of baseline versus follow-up continuous variables was performed with a paired t test. Comparison of nonparametric data between the two groups was performed with Wilcoxon test and Mann-Whitney test. Statistical analysis was performed with SPSS for Windows (version 10.1).

Results

Clinical data between the two groups did not differ significantly. The range of creatinine kinase levels was slightly but not significantly higher in the standard therapy group than it was in the cell therapy group (Table 1).

Comparison of the 2 groups 3 months after cell or standard therapy showed several significant differences in LV dynamics, according to the global and regional analysis of left ventriculogram. The infarct region as a percentage of hypokinetic, akinetic, or dyskinetic segments of the circumference of the left ventricle decreased significantly in the cell therapy group (from 30±13 to 12±7%, P=0.005). It was also significantly smaller compared with the standard therapy group after 3 months (P=0.04). Within the standard therapy group, only a statistically nonsignificant decrease from 25±8 to 20±11% could be seen. Wall movement velocity over the infarct region rose significantly in the cell therapy group (from 2.0±1.1 to 4.0±2.6 cm/s, P=0.028) but not in the standard therapy group (from 1.8±1.3 to 2.3±1.6 cm/s, P=NS). No significant difference was observed between the two groups. Ejection fraction increased in both groups, albeit nonsignificantly (from 57±8 to 62±10% in the cell therapy group and from 60±7 to 64±7% in the standard therapy group) (Table 2).

Further significant improvement could also be seen on additional analysis of the cell therapy group alone. Perfusion defect was considerably decreased by 26% in the cell therapy group (from 174±99 to 128±71 cm^2, P=0.016, assessed by ^{201}thallium scintigraphy) (Figure 2). Parallel to the reduction in perfusion defect, improvement (Table 3) could also be seen in:

(1) Cardiac function, as revealed by increase in stroke volume index (from 49±7 to 56±7 mL/m^2, P=0.010) and ejection fraction (from 51±14 to 53±13%, P=NS).
(2) Cardiac geometry, as shown by decreases in both end-diastolic (from 158±20 to 143±30 mL, P=NS) and end-systolic volume (from 82±26 to 67±21 mL, P=0.011). Radionuclide ventriculography was used to acquire the data.
(3) Contractility as evaluated by an increase in the velocity of circumferential fiber shortening (from 20.5±4.2 to 24.4±7.7 mm/s, P=NS, assessed by stress echocardiography) and by a marked increase in the ratio of systolic pressure to end-systolic volume (from 1.81±1.44 to 2.27±1.72 mm Hg/mL, P=0.005).

Discussion

The present report describes the first clinical trial of intracoronary, autologous, mononuclear BMC transplantation for improving heart function and myocardial perfusion in patients after acute MI. The results demonstrate that transplanted autologous BMCs may lead to repair of infarcted tissue when applied during the immediate postinfarction period. These results also show that the intracoronary approach of BMC transplantation seems to represent a novel

TABLE 2. Comparison of Cell Therapy and Standard Therapy Groups

	Cell Therapy	Standard Therapy	*P*
No. of patients	10	10	...
Infarct region as functional defect			
Hypokinetic, akinetic, or dyskinetic region at 0 mo, %	30±13	25±8	NS
Hypokinetic, akinetic, or dyskinetic region at 3 mo, %	12±7	20±11	0.04
P	0.005	NS	...
Contractility indices			
Infarction wall movement velocity at 0 mo, cm/s	2.0±1.1	1.8±1.3	NS
Infarction wall movement velocity at 3 mo, cm/s	4.0±2.6	2.3±1.6	NS
P	0.028	NS	...
Hemodynamic data			
LV ejection fraction at 0 mo, %	57±8	60±7	NS
LV ejection fraction at 3 mo, %	62±10	64±7	NS
P	NS	NS	...

NS indicates not significant; 0 mo, zero months, which means the time of infarction; 3 mo, 3 months, which means the time of the follow-up examinations. All data were obtained according to analysis of left ventriculogram.

and effective therapeutic procedure for concentrating and/or depositing infused cells within the region of interest.

Neogenesis of both cardiomyocytes and coronary capillaries with some functional improvement has been shown recently by several investigators using bone marrow–derived cells in experimental infarction.[11–14,18,20–23] Moreover, transendothelial migration from the coronary capillaries and incorporation of cells into heart muscle has been observed experimentally.[3,12,24–26] Until now, clinical data only existed for the cell therapy of surgically treated chronic ischemic heart disease.[15,16] Our aim was to transform the encouraging results from animal models to a safe clinical setting. The most crucial questions we had to address while designing and realizing this trial were: (1) What cell population should we deliver? (2) Which application method is the most efficient? (3) When should the cells be transplanted?

In recent years, several laboratories have shown that environmentally dictated changes of fate (transdetermination) are not restricted to stem cells but may also involve progenitor cells at different steps of a given differentiation pathway (transdifferentiation). Moreover, mesenchymal stem cells may represent an ideal cell source for treating different diseases.[27] Adult, mononuclear BMCs contain such stem and progenitor cells (≤1%), eg, mesodermal progenitor cells, hematopoietic progenitor cells, and endothelial progenitor cells. In several animal infarction models it has been shown that: (1) Bone marrow hemangioblasts contribute to the formation of new vessels; (2) bone marrow hematopoietic stem cells differentiate into cardiomyocytes, endothelium,

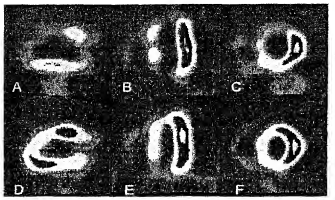

Figure 2. Improved myocardial perfusion of infarcted anterior wall 3 months after intracoronary cell transplantation subsequent to an acute anterior wall infarction detected by ^{201}thallium scintigraphy. The images on the left (A, D, sagittal) and in the middle (B, E) show the long axis, whereas those on the right (C, F, frontal) show the short axis of the heart. Initially the anterior wall, with green-colored apical and anterior regions, had reduced myocardial perfusion (A, B, C). Three months after cell transplantation the same anterior wall, now yellow in color, revealed a significant improvement in myocardial perfusion (D, E, F). All illustrations depict the exercise phase.

TABLE 3. Cardiac Function Analysis at 3-Month Follow-Up

	Before Cell Therapy	3 Months After Cell Therapy	*P*
No. of patients	10	10	...
Hemodynamic data			
LV ejection fraction, %	51±14	53±13	NS
Stroke volume index, mL/m^2	49±7	56±7	0.010
Cardiac geometry			
LV end-diastolic volume, mL	158±20	143±30	NS
LV end-systolic volume, mL	82±26	67±21	0.011
Contractility indices			
Circumferential fiber shortening, mm/s	20.5±4.2	24.4±7.7	NS
P_{sys}/ESV, mm Hg/mL	1.81±1.44	2.27±1.72	0.005
Infarct region as perfusion defect			
^{201}Thallium scintigraphy, cm^2	174±99	128±71	0.016

NS indicates not significant.

and smooth muscle cells[8-13]; (3) BMCs give rise to mesodermal progenitor cells that differentiate to endothelial cells[28]; and (4) endothelial progenitors can transdifferentiate into beating cardiomyocytes.[29] Thus, several different fractions of mononuclear BMCs may contribute to the regeneration of necrotic myocardium and vessels. In order to utilize this large and perhaps heterogeneous regenerative potential, we decided to use all mononuclear cells from the bone marrow aspirate as a whole, rather than a subpopulation. No further expansion was performed because experimental data have revealed a dramatic decline in the homing capacity of in vitro amplified hematopoietic stem or progenitor cells.[30]

The second question was how to deliver the cells most efficiently. When given intravenously, only a very small fraction of infused cells can reach the infarct region after the following injection: assuming a normal coronary blood flow of 80 mL/min per 100 g of LV weight, a quantity of 160 mL per left ventricle (assuming a regular LV mass of ≈200 g) will flow per minute.[31,32] This corresponds to only about 3% of cardiac output (assuming a cardiac output of 5000 mL/min).[31] Therefore, intravenous application would require many circulation passages to enable infused cells to come into contact with the infarct-related artery. Throughout this long circulation and recirculation time, homing of cells to other organs could considerably reduce the numbers of cells dedicated to cell repair in the infarcted zone. Thus, supplying the entire complement of cells by intracoronary administration obviously seems to be advantageous for the tissue repair of infarcted heart muscle and may also be superior to intraventricular injection,[33] because all cells are able to flow through the infarcted and peri-infarcted tissue during the immediate first passage. Accordingly, by this intracoronary procedure the infarct tissue and the peri-infarct zone can be enriched with the maximum available amount of cells at all times.

As stem cells differentiate into more mature types of progenitor cells, it is thought that a special microenvironment in so-called niches regulates cell activity by providing specific combinations of cytokines and by establishing direct cellular contact. For successful long-term engraftment, at least some stem cells have to reach their niches, a process referred to as homing. Mouse experiments have shown that significant numbers of BMCs appear in liver, spleen, and bone marrow after intravenous injection.[34] To offer the BMCs the best chance of finding their niche within the myocardium, a selective intracoronary delivery route was chosen. Presumably, therefore, fewer cells were lost by extraction toward organs of secondary interest by this first pass–like effect. To facilitate transendothelial passage and migration into the infarcted zone, cells were infused by high-pressure injection directly into the necrotic area, and the balloon was kept inflated for 2 to 3 minutes; the cells were not washed away immediately under these conditions.

The time point for delivery was chosen as 7 to 8 days after infarction onset for the following reasons:

(1) In dogs, infarcted territory becomes rich in capillaries and contains enlarged, pericyte-poor "mother vessels" and endothelial bridges 7 days after myocardial ischemia and reperfusion. Twenty-eight days later, a significant muscular vessel wall has already formed.[35] Thus, with such timing, cells may be able to reach the worst damaged parts and at the same time salvage tissue. Transendothelial cell migration may also be enhanced because an adequate muscular coat is not yet formed.

(2) Until now, only one animal study has attempted to determine the optimum time for cardiomyocyte transplantation to maximize myocardial function after LV injury. Adult rat hearts were cryoinjured and fetal rat cardiomyocytes were transplanted immediately, 2 weeks later, and 4 weeks later. The authors discussed the inflammatory process, which is strongest in the first days after infarction, as being responsible for the negative results after immediate cell transplantation, and they assumed that the best results seen after 2 weeks may have been due to transplantation before scar expansion.[36] Until now, however, no systematic experiments have been performed with BMCs to correlate the results of transplantation with the length of such a time delay.

(3) Another important variable is the inflammatory response in MI, which seems to be a superbly orchestrated interaction of cells, cytokines, growth factors and extracellular matrix proteins mediating myocardial repair. In the first 48 hours, debridement and formation of a fibrin-based provisional matrix predominates before a healing phase ensues.[37-40] Moreover, vascular endothelial growth factor is at its peak concentration 7 days after MI, and the decline of adhesion molecules (intercellular adhesion molecules, vascular cell adhesion molecules) does not take place before days 3 to 4 after MI. We assumed that transplantation of mononuclear BMCs within the "hot" phase of post-MI inflammation might lead them to take part in the inflammation cascade rather than the formation of functional myocardium and vessels.

Taking all of this into account, we can conclude that cell transplantation within the first 5 days after acute infarction is not possible for logistical reasons and is not advisable because of the inflammatory process. On the other hand, transplantation 2 weeks after infarction scar formation seems to reduce the benefit of cell transplantation. Although the ideal time point for transplantation remains to be defined, it is most likely between days 7 and 14 after the onset of MI, as in the present study.

This trial was designed as a phase I safety and feasibility trial, meaning that no control group is necessarily required. However, to validate the results, we correlated them with those obtained from 10 patients who refused to get additional cell therapy and thus received standard therapy alone. We are aware of the fact that such a comparison does not reach the power of a randomly allocated, blinded control group. However, the significant improvement with regard to infarct region, hemodynamics (stroke volume index), cardiac geometry (LV end-systolic volume), and contractility (P_{sys}/ESV and infarction wall movement velocity) did confirm a positive effect of the additional cell therapy because the changes observed in the standard therapy group failed to reach significance.

Another important factor for interpreting the results is time interval between onset of symptoms and revascularization of the infarct-related artery by angioplasty; this represents a crucial determinant of LV recovery. For patients with acute MI, it has

been shown that if the time interval is >4 hours, no significant changes in ejection fraction, regional wall motion, or ESV are observed after 6-month follow-up by echocardiography and angiography.[41] None of our 20 patients was treated by angioplasty within 4 hours after onset of symptoms. Our average time interval was 12±10 hours. Thus, PTCA-induced improvement of LV function can be nearly excluded; indeed, the only mild and nonsignificant changes within the standard therapy group are consistent with the above-mentioned data.[41] In contrast, the cell therapy group showed considerable and significant improvement in the same parameters, which may be attributed to BMC-mediated coronary angioneogenesis and cardiomyoneogenesis.

These results show that transplantation of autologous BMCs, as well as the intracoronary approach, represent a novel and effective therapeutic procedure for the repair of infarcted myocardium. For this method of therapy, no ethical problems exist, and no side effects were observed at any point of time. The therapeutic benefit for the patient's heart seems to prevail. However, further experimental studies, controlled prospective clinical trials, and variations of cell preparations are required to define the role of this new approach for the therapy of acute MI in humans.

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Related Articles, Links

ELSEVIER SCIENCE
FULL-TEXT ARTICLE

Viability and differentiation of autologous skeletal myoblast grafts in ischaemic cardiomyopathy.

Hagege AA, Carrion C, Menasche P, Vilquin JT, Duboc D, Marolleau JP, Desnos M, Bruneval P.

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Autologous skeletal myoblast transplantation might improve postinfarction ventricular function, but graft viability and differentiation (ie, proof of concept) has not been shown. A 72-year-old man had autologous cultured myoblasts from his vastus lateralis injected to an area of transmural inferior myocardial infarction in non-reperfused scar tissue. He showed improvement in symptoms and left-ventricular ejection fraction. When he died 17.5 months after the procedure, the grafted post-infarction scar showed well developed skeletal myotubes with a preserved contractile apparatus. 65% of myotubes expressed the slow myosin isoform and 33% coexpressed the slow and fast isoforms (vs 44% and 0.6%, respectively, in skeletal muscle). Myoblast grafts can survive and show a switch to slow-twitch fibres, which might allow sustained improvement in cardiac function.

PMID: 12583951 [PubMed - indexed for MEDLINE]

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myocardial tissue. These results establish the feasibility of myoblast transplants for myocardial repair in humans.

Publication Types:
- Clinical Trial
- Clinical Trial, Phase I

PMID: 12628737 [PubMed - indexed for MEDLINE]

Medscape Medical News

Autologous Cell Transplant Helpful in Ischemic **Heart** or Legs

Laurie Barclay, MD

Nov. 18, 2002 — Autologous cell transplantion may benefit ischemic hearts and legs, according to three presentations on Nov. 18 at the American **Heart** Association's 75th Scientific Sessions held in Chicago, Illinois. Two studies focused on injecting autologous bone marrow cells or autologous skeletal myoblasts into the scarred area of an infarcted **heart**. In another study, injecting autologous bone marrow into ischemic limbs led to new vessel growth, reducing the need for amputation.

"Bone marrow not only can differentiate into **heart** cells, but also smooth muscle cells, connective **tissue** cells and other types of cells to reconstitute the entire structure of a **tissue**," presenter Manuel Galinanes, MD, from the University of Leicester in the U.K., says in a news release. "The benefit [of transplanting bone marrow into scar **tissue** of the **heart**] could be seen only six weeks **after** injection."

In 14 patients with low ejection fraction post-myocardial infarction (MI), autologous bone marrow from the sternum was injected into scarred myocardium during nonemergency coronary artery bypass surgery. **Heart** wall motion measured with echocardiography improved within weeks of treatment, and improvements persisted for at least 10 months **after** treatment.

The regional wall motion score decreased significantly, reflecting less movement abnormality, from a mean score of 2.41 at baseline to 2.16 six weeks **after** treatment and 2.09 ten months **after** treatment. The global wall motion score also decreased significantly from 1.96 before surgery to 1.64 at six weeks, and stabilized at 1.65 **after** 10 months.

Although it is still unproven that bone marrow creates a new cellular infrastructure in **heart** scar **tissue**, "that is the only possible explanation," Galinanes says. "The ability to confirm the presence of scar **tissue** with dobutamine stress echo before surgery, and then confirm it again during surgery, told us that the affected area was dysfunctional and the abnormality was irreversible. We wanted to make sure that we were injecting the marrow into **dead tissue** to help ensure that the injection would not pose any serious risk to the patient."

If additional studies confirm safety and efficacy, Galinanes says that this treatment would be a welcome addition to the post-MI arsenal, which also includes gene therapy, growth factor therapy, and laser treatments.

In a multicenter trial supervised by the U.S. Food and Drug Administration, investigators safely transplanted 16 patients with autologous skeletal myoblasts injected into hearts severely damaged by MI or **heart** failure. Baseline left-ventricular ejection fraction was less than 30%. Eleven patients were undergoing coronary artery bypass surgery and five were having implantation of a left ventricular assist device. Myoblasts extracted from thigh muscle were grown in large quantities in vitro using a controlled cell expansion manufacturing process, and were injected in doses ranging from 10 million to 300 million cells.

"We have been able to **regenerate dead heart** muscle, or scar **tissue**, in the area of **heart** attack without increasing risk of death. Our findings will allow us to move forward with testing if the procedure can improve the contractility of the **heart**," says lead author Nabil Dib, MD, from the Arizona **Heart** Institute in Phoenix. "We found that the transplanted myoblasts survived and thrived in patients. Areas damaged by **heart** attack and cardiovascular disease showed evidence of repair and viability."

Twelve weeks **after** transplant, mean ejection fraction rates improved from 22.7% to 35.8%, or a 58% increase. Echocardiogram, magnetic resonance imaging, and positron emission tomography showed evidence of regeneration in the area of the graft. There were no significant adverse events related to the cell transplant procedure at nine-month follow-up.

The third study showed that bone marrow cells implanted into ischemic legs in patients with peripheral arterial disease (PAD) formed new blood vessels, increased blood flow, and prevented amputation.

"This is the first multicenter and double-blind clinical study to prove the clinical efficacy of growing new blood vessels (angiogenesis) using bone marrow cell transplantation," says lead author Hiroya Masaki, MD, PhD, from Kansai Medical University in Osaka, Japan.

In this randomized trial, 45 patients with PAD received injections of autologous bone marrow mononuclear cells into the calf muscles. Compared with controls who received saline injections, patients who received bone marrow mononuclear cell transplants had a "striking" increase in new capillary formation and in newly visible collateral vessels.

Of 45 treated patients, 31 had an increase in ankle-brachial pressure index in the treated limbs, and 39 had decreased rest pain with improved treadmill endurance. Ischemic ulcers or gangrene healed in 21 of 28 treated limbs.

CD34-cells, which can develop into endothelial progenitor cells, expressed angiogenic growth factors including basic fibroblast growth factor, vascular endothelial growth factor, and angiopoietin-1. Although more research is needed to determine long-term efficacy and safety, "this new angiogenesis therapy using bone marrow cell transplantation may help many patients suffering with ischemic limbs," Masaki says.

AHA 75th Scientific Sessions: Abstracts 111623, 101758, 109801. Presented Nov. 18, 2002.

Reviewed by Gary D. Vogin, MD

1: J Am Coll Cardiol 2003 Mar 5;41(5):879-88

Related Articles, Links

ELSEVIER SCIENCE
FULL-TEXT ARTICLE

Autologous skeletal myoblasts transplanted to ischemia-damaged myocardium in humans. Histological analysis of cell survival and differentiation.

Pagani FD, DerSimonian H, Zawadzka A, Wetzel K, Edge AS, Jacoby DB, Dinsmore JH, Wright S, Aretz TH, Eisen HJ, Aaronson KD.

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OBJECTIVES: We report histological analysis of hearts from patients with end-stage heart disease who were transplanted with autologous skeletal myoblasts concurrent with left ventricular assist device (LVAD) implantation. BACKGROUND: Autologous skeletal myoblast transplantation is under investigation as a means to repair infarcted myocardium. To date, there is only indirect evidence to suggest survival of skeletal muscle in humans. METHODS: Five patients (all male; median age 60 years) with ischemic cardiomyopathy, refractory heart failure, and listed for heart transplantation underwent muscle biopsy from the quadriceps muscle. The muscle specimen was shipped to a cell isolation facility where myoblasts were isolated and grown. Patients received a transplant of 300 million cells concomitant with LVAD implantation. Four patients underwent LVAD explant after 68, 91, 141, and 191 days of LVAD support (three transplant, one LVAD death), respectively. One patient remains alive on LVAD support awaiting heart transplantation. RESULTS: Skeletal muscle cell survival and differentiation into mature myofibers were directly demonstrated in scarred myocardium from three of the four explanted hearts using an antibody against skeletal muscle-specific myosin heavy chain. An increase in small vessel formation was observed in one of three patients at the site of surviving myotubes, but not in adjacent tissue devoid of engrafted cells. CONCLUSIONS: These findings represent demonstration of autologous myoblast cell survival in human heart. The implanted skeletal myoblasts formed viable grafts in heavily scarred human